UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,802	09/17/2001	Roland Kreutzer	33796	8835

29933 7590 06/25/2003

PALMER & DODGE, LLP
KATHLEEN M. WILLIAMS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	24

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,802	KREUTZER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *221-225,232-239,241-245 and 247* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *221-225,232-239,243,245 and 247* is/are rejected.

7)☒ Claim(s) *241,242,244* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22,23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 221-225, 232-2339, 241-245 and 247 are pending.

Applicants' traversal, the amendment to claims 221, 222, 224, 225, 241, and 243, the amendment to the specification, the cancellation of claims 226-231, 240, and 246 in paper no. 21 filed on 4/20/03 is acknowledged and considered.

In the last office actions filed on 4/7/03, it was stated that Claims 240, 244, 246, and 247 are objected to as being dependent upon a rejected base claim (claims 232 and 221), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. However, upon further search of the prior art, claims 240 and 246 (now amended claims 231 and 232, respectively) are not considered novel for the reasons set forth under the new 102 rejection.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in German on 1/30/99 and 11/24/99. It is noted, however, that applicant has not filed a certified copy of the 19903713.2 and 19956568.6 applications as required by 35 U.S.C. 119(b).

Specification

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to objections to the specification have been fully considered and are persuasive. The objections to the specification have been withdrawn.

Claim Objections

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to objection have been fully considered and are persuasive. The objection to claim 243 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 232-238, 245, and 247 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mammalian cell comprising an exogenous oligoribonucleotide wherein the oligoribonucleotide has a double stranded RNA (dsRNA) comprising two separate RNA strands, wherein the dsRNA comprises a 3' overhang, and wherein one strand of has a region which is complementary to an RNA transcript of at least a part of a target gene, does not reasonably provide enablement for a mammalian cell comprising the exogenous oligoribonucleotide. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 232-238, 245 and 247 are drawn broadly to making and using a mammalian cell comprising the claimed oligoribonucleotide.

The specification provides examples wherein the inhibition of transcription of a target gene was detected in an *in vitro* transcription system. The specification has not provided any examples wherein an oligoribonucleotide is delivered to a mammalian cell *in vivo*.

At the time of the invention, using a mammalian cell *in vivo* was highly unpredictable, mainly due to issues of how specifically deliver a nucleic acid molecule to a target gene in a mammal at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell to achieve and maintain expression of the gene. Gene therapy methods are further hampered by unpredictable loss of expression (see example Branch, TIBS Vol. 23 45-50, 1998; Anderson, Nature, Vol. 392, 25-30, 1998; and Verma et al., Nature, Vol. 389, 239-242, 1997). The mammalian cells require a dsRNA be delivered specifically to a target mammalian cell at a concentration effective enough to inhibit the expression of a target gene. As such, although Branch, Agrawal et al., Molecule Medicine Vol. 6, 72-81, 2000, Verma and Anderson discuss issues of delivery and expression in reference to antisense methods and gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed mammalian cells. The specification provides guidance with respect to delivery of dsRNA into cells *in vitro*, however, the specification does not provide any

specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of a dsRNA in any mammalian cell. The guidance provided for in vitro would not be expected to translate into generally any in vivo mammalian cell because the conditions are very different. For example, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of dsRNA in vivo.

To use the claimed mammalian cells, over the full scope claimed, it would require undue amount of experimentation for one skilled in the art. Such experimentation would include the determination of how to specifically deliver the dsRNA to the a mammalian cell at a concentration effective to inhibit the expression of a target gene, the determination of an appropriate route of administration for each target cell type "the search for such combination is a case of trial and error for a given type of cell." (See Verma, page 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor (beyond isolated mammalian cells, the lack of working examples (beyond cell culture data), and the quantity of experimentation that would be required, it would required undue experimentation, beyond what is taught in the specification, to use the cells as claimed over the full scope claimed.

Applicants' arguments with respect to claims 232-238, 245 and 247 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection to claims 241 and 242 has been withdrawn.

Claim Rejections - 35 USC § 102

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to 102(e) rejection have been fully considered and are persuasive. The rejection to Claims 221, 222, 224, and 243 are rejected under 35 U.S.C. 102(e) as being by Shimkets et al. (US 6,486,299, EFD 9/28/98) has been withdrawn because of the amendment to claim 221.

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to 102(e) rejection have been fully considered and are persuasive. The rejection to Claims 221, 222, 223, 232, 233, 234, 235, 236, and 243 are rejected under 35 U.S.C. 102(e) as being by Fire et al. (US 6,506,559, EFD 12/23/97) has been withdrawn because of the amendment to claims 221 and 232.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 221, 223, and 224 are rejected under 35 U.S.C. 102(b) as being anticipated by Alfonzo et al. (Nucleic Acid Research, Vol. 25, 3751-3759, 1997). Alfonzo teaches a double stranded RNA (dsRNA), wherein one strand has a region which is complementary to an RNA transcript of at least part of a mammalian gene, and the dsRNA comprises a 3' overhang, wherein the RNA strands are linked together (page 3755).

Applicants' arguments with respect to claims 221 and 223 have been considered but are moot in view of the new ground(s) of rejection.

Claims 221, 222, 223, 224, 225, 232, 233, 234, 235, 236, 237, 238, 239, 243, and 245 are rejected under 35 U.S.C. 102(e) as being anticipated by Kmiec et al. (US Patent 6,573,046, EFD 5/12/98). Kmiec teaches a recombinagenic oligonucleobase characterized by being a duplex nucleotide, including nucleotide derivatives or non-nucleotide interstrand linkers, and having between 20 and 120 nucleobases or equivalently between 10 and 60 Watson-Crick nucleobase pairs (column 4). In a preferred embodiment, the recombinagenic oligonucleobase is substantially a duplex and contains a single 3' end and 5' end; accordingly, the strands of the duplex are covalently linked by oligonucleobase or non-oligonucleobase linkers (column 4 and column 11). A further embodiment of the present invention is based on the discovery that the Non-Chimeric Mutational Vector (NCMV), according to Kumar, are effective substrates for the strand transfer and repair enzymes of eukaryotic and, specifically mammalian cells (column 4

and column 15). Kmiec further teaches that nucleobases are ribo-type (column 7 and column 8, lines 47-61). Furthermore, Kmiec teaches that the first and second strands consist of at least two regions that are homologous to a target gene, preferably between 30 and 45 (column 8, lines 26-46). In addition, Kmiec teaches that the oligonucleobase can have a 3' overhang (column 10, lines 40-67). The oligonucleobase can comprise a nuclease resistant nucleobase or 3' exonuclease protection or a polyethylene glycol linker (column 9, line 29-column 10, line 39).

Applicants' arguments with respect to claims 221, 222, 223, 224, 225, 232, 233, 234, 235, 236, 237, 238, 239, 243, and 245 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to 103(a) rejection have been fully considered and are persuasive. The rejection to Claims 221, 232, 239, and 245 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 6,506,559, EFD 12/23/97) taken with Pasloske et al. (US Patent 5,939,262, EFD 6/24/97) has been withdrawn because of the amendment to claims 221 and 232.

Applicant's arguments, see paper no. 21, filed on 4/20/03, with respect to 103(a) rejection have been fully considered and are persuasive. The rejection to Claims 221, 224, 225, 232, 237, and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 6,506,559, EFD 12/23/97) taken with Jaschke et al., (Nucleosides & Nucleotides, Vol. 15, pages 1519-1529, 1996).

Conclusion

Claims 241, 242, and 244 are free of the prior art.

Claims 241, 242 and 244 are objected to as being dependent upon a rejected base claim (claim 221), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER